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RESEARCH ARTICLE

The Familial Risk of Autism Spectrum Disorder with and without Intellectual Disability

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Autism spectrum disorder (ASD) is highly heritable, yet how its familial risk and heritability may vary by cognitive ability is not well understood. In this population-based cohort study, we examined the familial risk and heritability of ASD with and without co-occurring intellectual disability (ID). We estimated odds ratios and heritability of ASD with ID (ASD+ID) and ASD without ID (ASD-ID) using register-based diagnosis data of 567,436 index persons born in 1984–2009 in Stockholm County, Sweden, and their parents, siblings, cousins, aunts, and uncles. The familial risk profile exhibited differences between ASD-ID and ASD+ID, most notably for index persons with affected parents. For example, for an index person who had at least one parent with ASD, the child's odds of ASD-ID and ASD+ID (95% confidence interval (CI)) increased by 16.2 (14.2–18.6) and 7.4 (5.5–10.0) folds, respectively. The more closely related a family member with ASD was, the greater the observed risk was of ASD in the index person, especially for ASD-ID. The broad-sense heritability (95% CI) for ASD-ID and ASD+ID were 64.6% (46.0–100.0%) and 33.4% (14.4–58.4%), respectively. Familial risk and heritability of ASD may vary by intellectual ability, which implies that risk factors between these ASD phenotypes may differ. Our findings from the heritability analysis and familial risk analysis suggest that ASD-ID may have a greater genetic basis than ASD+ID, although this should be verified in future studies. *Autism Res* 2020, 00: 1–9. © 2020 The Authors. *Autism Research* published by International Society for Autism Research and Wiley Periodicals LLC.

Lay Summary: Autism spectrum disorder (ASD) is highly heritable, yet how its familial risk and heritability may vary by cognitive ability is not well-understood. In a population-based cohort study on families of 567,436 index persons using Swedish registers data, we found that the familial risk profile differed between ASD with and without intellectual disability. Our findings from the heritability analysis and familial risk analysis suggest that ASD-ID may have a greater genetic basis than ASD+ID, although this should be verified in future studies.

Keywords: autism spectrum disorders; intellectual disability; heritability; familial risk; family study

Introduction

Autism spectrum disorders (ASD) are a group of heterogeneous and highly familial neurodevelopmental disorders with early onset that affects 1–2% of the population worldwide [Idring et al., 2012; Newschaffer et al., 2007]. Family history is strongly associated with ASD risk. For example, a study by Sandin et al. observed that having a full sibling or co-twin with ASD was associated with a 10.3- to 153.0-fold increase in a child's risk of ASD [Sandin et al., 2014]. Heritability of ASD is sizable, with most estimates ranging from 50–90% in the literature

[Bai et al., 2019; Gaugler et al., 2014; Tick, Bolton, Happé, Rutter, & Rijdsdijk, 2016].

Less is known about how the familial risk and heritability of ASD may vary by intellectual ability. Approximately 25% of individuals with ASD have co-occurring intellectual disability (ID, defined as IQ < 70) [Idring et al., 2015], and differences between individuals with ASD-ID and ASD+ID have been observed with regards to behavior [Matson & Shoemaker, 2009; Wilkins & Matson, 2009], family psychiatric history [Robinson et al., 2014], genetics [Robinson et al., 2014], co-occurring disorders [Hallett et al., 2013; Rai et al., 2018], parental age [Idring

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et al., 2014], paternal intelligence [Gardner et al., 2019], maternal health [DeVilbiss et al., 2017; Lee et al., 2015; Magnusson et al., 2016] and medication use during pregnancy [Rai et al., 2013, 2017], pre- and perinatal characteristics [Abel et al., 2013; Schieve, Clayton, Durkin, Wingate, & Drews-Botsch, 2015; Xie et al., 2017], as well as socioeconomic and demographic factors [Becerra et al., 2014; Delobel-Ayoub et al., 2015; Fairthorne, de Klerk, Leonard, Schieve, & Yeargin-Allsopp, 2017; Magnusson et al., 2012]. These observations have led to the hypothesis that these ASD phenotypes might be etiologically different.

This hypothesis has been tested in recent studies using genetic data, and findings are accumulating in support of it. Studies in clinical collections such as the Simons Simplex Collection suggested that a positive family history of psychiatric disorders was more common among individuals with ASD without ID (ASD-ID) than among those with ASD and ID (ASD+ID). The latter group appeared less familial and instead more often harbored *de novo* mutations, that is, mutations not detected among their immediate family members [Robinson et al., 2014]. Gaugler et al. observed a higher SNP-heritability of ASD with IQ > 80 compared to that of ASD overall [Gaugler et al., 2014]. Grove et al. reported a three-fold higher SNP-heritability for ASD-ID as compared to ASD+ID [Grove et al., 2019].

Individuals with ASD-ID and ASD+ID often require different support and have different life outcomes [Lord, Elsabbagh, Baird, & Veenstra-Vanderweele, 2018]. Therefore, it is important to address these questions regarding etiology that may impact future research and practice. In this study, we examined the familial risk and heritability of ASD by the presence/absence of co-occurring ID, using population register data on first- to fourth-degree kin in Sweden. The rationale was that if ASD with and without ID were etiologically different, then their familial risk profiles would also exhibit differences.

Method

Study Population

We used prospectively collected data across national and regional health and administrative registers linked by unique personal identification numbers (PIN) assigned to each Swedish resident. All data were anonymized by Statistics Sweden before being received by the research team. Individual PINs were replaced by a unique study-specific identification code, which protected the personal integrity of the individuals. The key between the PIN and the study-specific identification code was kept exclusively by Statistics Sweden. Ethical approval was provided by the Research Ethics Committee of Stockholm County

Council. Informed consent was not required for the analysis of anonymized register data.

Index persons were identified from the Stockholm Youth Cohort, an ongoing longitudinal register-linkage cohort study of the total child population aged 0–17 years residing in Stockholm County, Sweden, who were born between 1984 and 2009 [Idring et al., 2012]. Index persons included in this study were non-adopted singleton births who were at least 2 years of age at the end of follow-up on December 31, 2011, and could be linked to both biological parents. In Sweden, developmental surveillance is performed by specially trained child healthcare center nurses at regular intervals (1, 2, 6, 10–12, 18, 36, 48 and 60 months of age) and engages almost all pre-school children. The purpose of developmental surveillance is to ensure timely discovery of developmental problems such as cerebral palsy, speech disorders, ASD, intellectual disabilities, and ADHD [Idring et al., 2012]. Early behavioral signs of ASD emerge in the first 2 years of life [Sacre, Bennett, & Zwaigenbaum, 2015]. We required all persons to be at least 2 years old by the date of the last follow-up to ensure opportunity for detection. The Multi-Generation Register links parents to children for all children born from 1932 onwards [Ekbom, 2011]. This allowed us to determine family relations for each index person including fathers, mothers, brothers, sisters, half-brothers, half-sisters, uncles, aunts, half-uncles, half-aunts, first cousins, and half-cousins (Fig. 1). In addition, we required all index persons and their relatives included in the study to have at least 2 years of residence in Sweden to ensure entry of diagnoses into the registers.

Diagnoses Ascertainment

ASD-ID and ASD+ID were defined as having a positive ASD diagnosis without or with an ID diagnosis from birth to death, emigration, or the latest register update on December 31, 2011, whichever occurred first. ASD and ID statuses of the index persons were ascertained using four national and regional registers covering all known pathways of ASD diagnosis and care in Stockholm County – Habilitation Register (since 1998), Clinical Database for Child and Adolescent Psychiatry in Stockholm (since 2001), the VAL databases (since 1997), and the National Patient Register (since 1964, with nearly complete coverage for psychiatric clinics from 1973 onwards). For the relatives, the data on diagnoses were obtained from the National Patient Register.

Diagnoses were ascertained using International Classification of Diseases (ICD) and Diagnosis and Statistical Manual of Mental Disorders (DSM) codes and health services records. Diagnosis codes for ASD were F84 (ICD-10) and 299 (ICD-9). Diagnosis codes for ID were F70-79 (ICD-10), 317–319 (ICD-9), and 310–315 (ICD-8). In our

sample, ASD was identifiable in records from 1987 onwards and was diagnosed in persons born as early as 1922. Vital statistics were obtained from the Cause of Death Register. Validation studies on the diagnoses of ASD+ID and ASD-ID in the Stockholm Youth Cohort and diagnoses in the National Patient Register showed that these diagnoses had high test/retest reliability [Dalman, Broms, Cullberg, & Allebeck, 2002; Idring et al., 2012; Rück et al., 2015; Sellgren, Landén, Lichtenstein, Hultman, & Långström, 2011].

Statistical Methods

Relative familial risk. We refer to odds ratio (OR) as the measure of relative risk. The outcomes of interest were ASD-ID and ASD+ID in the index persons. To examine the association between each outcome in index persons and ASD diagnosis in relatives, we fitted one logistic regression model for each type of relation and calculated the two-sided 95% Wald-type confidence intervals. We considered several factors that might confound the familial associations in the estimation of familial risk. Secular trends were adjusted for using birth years of the index persons and relatives. To account for the high male prevalence in ASD, especially in ASD-ID, we included sex as a covariate in models as well as modeled the outcomes in male and female index persons separately. We calculated ORs and Huber-White robust standard errors accounting for family clusters using the *rms* package [Harrell Jr, 2015].

Heritability. In the unadjusted analysis, we used tetrachoric correlation coefficients to describe the unadjusted heritability as quantified by the association of index person's ASD+ID and ASD-ID status with ASD diagnosis in relatives.

For estimating the adjusted heritability of ASD+ID and ASD-ID, we fitted an ACDE liability-threshold model [Griffiths et al., 2000] to the diagnosis of index persons and their first- and second-degree relatives (full siblings, half-siblings, parents, aunts and uncles). The total phenotypic variance V_P of a heritable trait can be thought of as the sum of two component variances, one genetic and one environmental, which can then be further decomposed into additive heritable genetic (V_A), non-additive non-inheritable genetic (V_D), common environmental (V_C), and unique environmental components (V_E). Details of the model were presented in the Appendix S1. Briefly, first, the diagnosis of the index persons was regressed onto the covariates (index person's sex and birth year, and relative's birth year) in a probit model. Then, the part of variance in the outcome that was not explained by the covariates was decomposed into four latent components (V_A , V_D , V_C , V_E) based on maximum likelihood estimates. Our a priori choice of these

components of heritability to include in the model was based on the best supported etiological model of ASD by evidence to date [Gaugler et al., 2014; Robinson et al., 2014; Sandin et al., 2017; Tick et al., 2016]. To evaluate the robustness of the model, we conducted a sensitivity analysis on the covariance specification by varying the assumption about the common environmental component.

Tetrachoric correlation coefficients were estimated using the *polycor* package [Fox & Fox, 2016]. The heritability modeling was implemented using *OpenMx*, version 2.8.3 [Neale et al., 2016]. Analyses were performed in R 3.4.3 (R Development Core Team, 2016).

Results

The cohort included 567,436 unique, non-adopted singleton index persons who were born in Stockholm County, Sweden between January 1, 1984, and December 31, 2009, resided there for at least 2 years by the end of follow-up on December 31, 2011, and could be linked to both biological parents. The index persons' mean (SD) age at the end of follow-up was 14.3 (7.5) years. The earliest year of birth for parents, siblings, aunts/uncles, and cousins was 1911, 1938, 1932 and 1948, respectively. The mean (SD) age at diagnosis of ASD without ID for index persons' fathers and mothers was 42.2 (9.6) and 39.2 (9.3) years, respectively. The mean (SD) age at diagnosis of ASD without ID among aunts and uncles ranged from 23.4 (13.8) years for half-uncles to 37.3 (11.4) years for aunts. The mean (SD) age at diagnosis of ASD with ID for index persons' fathers and mothers was 32.3 (14.2) and 34.7 (14.4) years, respectively. The mean (SD) age at diagnosis of ASD with ID among aunts and uncles ranged from 15.8 (11.3) years for half-uncles to 31.3 (14.0) years for aunts. The median (IQR) family size of index persons was 15 (10–19) relatives. Among the index persons, there were 2,566 persons with ASD+ID and 8,354 with ASD-ID. ASD prevalence among relatives of ASD-ID index persons was higher than that among relatives of ASD+ID index persons for most relations (Table 1). Numbers of index person-relative pairs are provided in Figure 1.

Familial Risk of ASD without ID

The size of the familial risk of ASD-ID varied by the degree of relatedness between the index persons and the affected relative, with the familial risk being higher if the affected relative was a closer relative (Fig. 2, Table S1). Having a mother with ASD was associated with a 19.6-fold increase in the odds of ASD-ID in the index persons compared to those with unaffected mothers, and having an affected father was associated with a 12.0-fold

Table 1. Prevalence of Autism Spectrum Disorders with and without Intellectual Disability in Relatives of Affected and Unaffected Index Persons

Family relations	ASD in relatives of IPs without ASD		ASD in relatives of IPs with ASD–ID		ASD in relatives of IPs with ASD+ID	
	<i>n</i>	<i>n</i> per 1,000 persons	<i>n</i>	<i>n</i> per 1,000 persons	<i>n</i>	<i>n</i> per 1,000 persons
First-degree relatives						
Father	501	0.9	91	10.9	7	2.7
Mother	610	1.1	188	22.5	39	15.2
Brother	7,880	21.6	646	129.7	251	135.5
Sister	3,103	9.0	339	71.2	103	61.6
Second-degree relatives						
Uncle	2,706	4.0	88	8.5	20	7.1
Aunt	1,668	2.6	44	4.4	8	3.1
Half-brother	3,830	25.5	195	59.1	55	62.6
Half-sister	1,687	11.8	88	28.5	22	25.1
Third-degree relatives						
Half-uncle	2,440	10.2	75	16.7	22	20.1
Half-aunt	1,325	5.8	32	7.1	9	8.5
First-cousin, male	20,389	17.8	541	30.6	137	27.2
First-cousin, female	8,799	8.2	234	14.1	52	11.2
Fourth-degree relatives						
Half-cousin, male	5,941	19.4	156	26.3	31	19.4
Half-cousin, female	2,785	9.5	59	10.2	13	8.7

ASD–ID: autism spectrum disorders without intellectual disability; ASD+ID: autism spectrum disorders with intellectual disability; IP: index person.

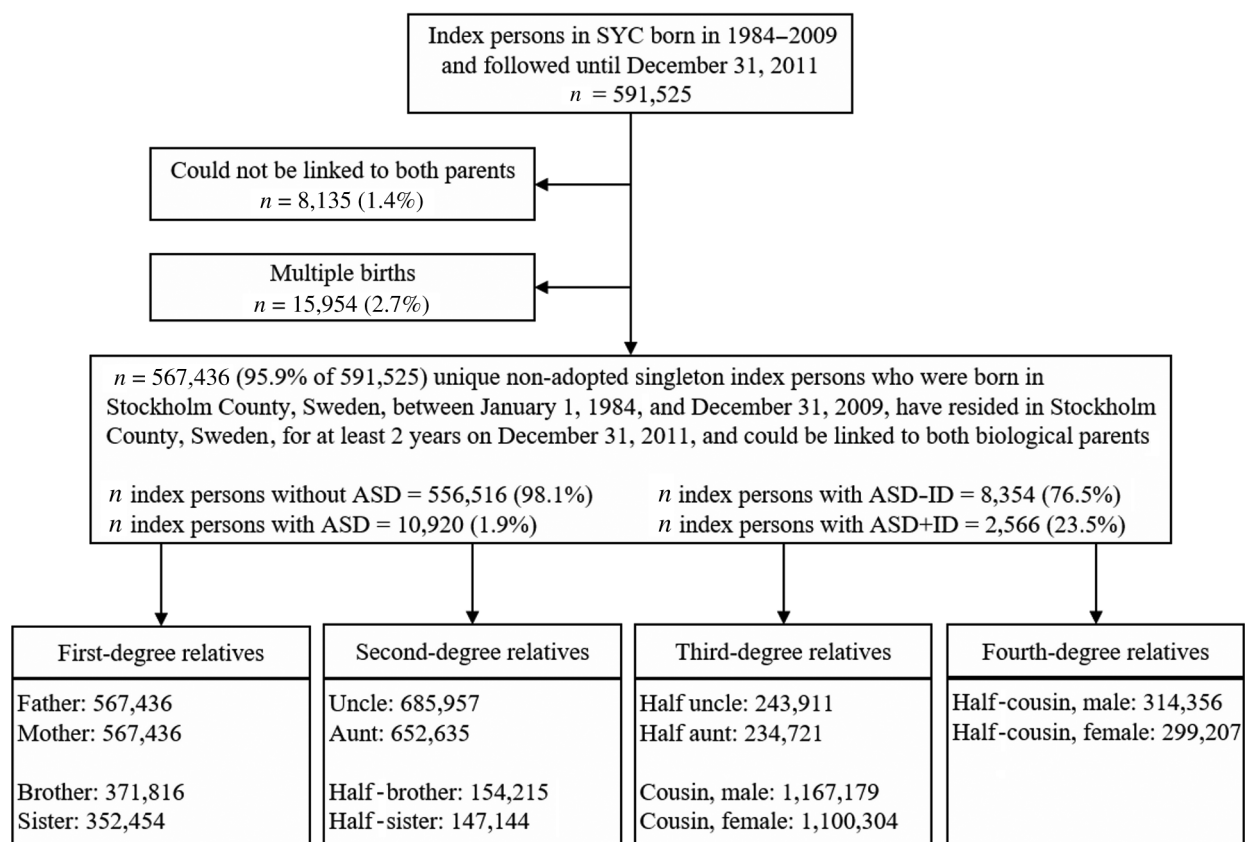


Figure 1. Selection of index persons from the Stockholm Youth Cohort and pedigree ascertainment. ASD–ID: autism spectrum disorders without intellectual disability; ASD+ID: autism spectrum disorders with intellectual disability; SYC: Stockholm Youth Cohort.

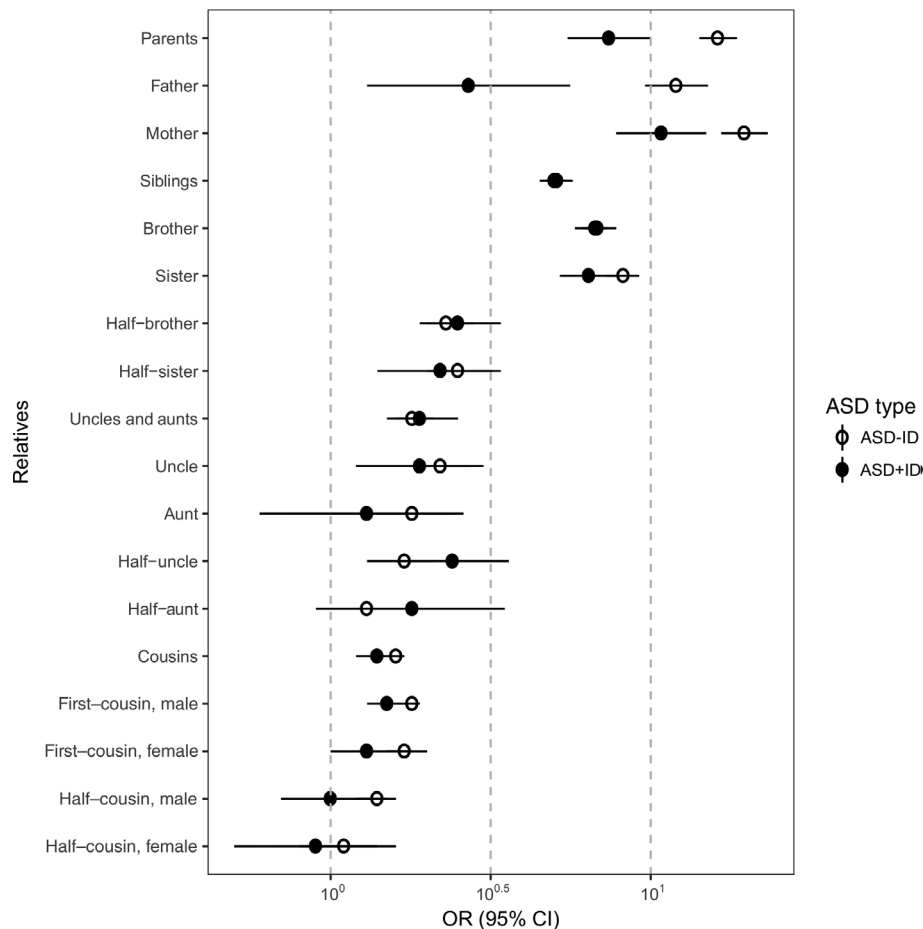


Figure 2. Odds ratio of autism spectrum disorders with and without intellectual disability in all index persons, with relatives affected by ASD, compared to that in index persons with unaffected relatives. ASD-ID: autism spectrum disorders without intellectual disability; ASD+ID: autism spectrum disorders with intellectual disability; CI: confidence interval; OR: odds ratio. *Note.* “Parents” included fathers and mothers; “siblings” include full- and half-siblings; “uncles and aunts” included full- and half-uncles and aunts; and “cousins” included first- and half-cousins.

Table 2. Heritability of Autism Spectrum Disorders with and without Intellectual Disability

	ASD-ID	ASD+ID
Heritability estimates, % (95% CI) ^a		
Total genetic	64.6 (46.0–100.0)	33.4 (14.4–58.4)
Total environmental	35.4 (0.0–54.0)	66.6 (41.6–85.6)

See Appendix S1 for details regarding calculation of heritability.
ASD-ID: autism spectrum disorders without intellectual disability; ASD+ID: autism spectrum disorders with intellectual disability; CI: confidence interval; IP: index person.
^aCIs were calculated from 500 sets of bootstrap samples.

increase. In contrast, having an affected cousin was associated with less than doubled risk of ASD-ID in the index persons. This trend of higher risk in index persons with

affected first-degree female relatives was consistent across male and female index persons (Table S1).

Familial Risk of ASD with ID

As in ASD-ID, family history of ASD was associated with higher risk of ASD+ID in the index persons, especially if the affected relative was closer relative (Fig. 2, Table S1). Although the magnitude of the familial risk was similar between ASD+ID and ASD-ID for most relative types, ORs for parents differed notably between the two ASD phenotypes. Having a mother with ASD was associated with 10.8-fold increased odds of ASD+ID in the index persons compared to those with an unaffected mother. This was less than half the size of the OR associated with ASD-ID in index persons with an affected mother. The size of the familial risk associated with having an affected father was also smaller for ASD+ID than for ASD-ID. This

trend was similar between male and female index persons (Table S1).

Heritability of ASD with and without ID

The tetrachoric correlations (r_t) were unadjusted estimates of the correlation of index person's ASD+ID and ASD-ID diagnosis with family relative's ASD diagnosis. r_t was higher for ASD-ID than for ASD+ID, and higher for closer kin than for more distant kin (Table S2).

Heritability estimates are shown in Table 2. The total genetic component (i.e., broad-sense heritability) accounted for 64.6% (95% CI: 46.0–100.0%) and 33.4% (95% CI: 14.4–58.4%) of the liability of ASD-ID and ASD+ID, respectively. Estimates from the sensitivity analysis testing varying assumptions regarding the amount of shared environment were nearly identical to those reported in Table 2, with differences being <2% between all point estimates (results not shown).

Discussion

This study is a first investigation on the familial risk and heritability of ASD+ID and ASD-ID using data on one large set of extended families ascertained from population-based registers in Sweden. While familial risk clearly contributed to both ASD+ID and ASD-ID, we observed some differences in the risk profile between ASD+ID and ASD-ID, especially the risk associated with having affected parents. Also, for both ASD phenotypes, the risk of index persons increased with kinship proximity of the affected relative.

While we observed a higher estimate of heritability of ASD-ID than for ASD+ID, the imprecision of the estimates necessitates further investigation. Previous research has reported clinical differences, and differences in prevalence and risk factors between these phenotypes [Abel et al., 2013; Becerra et al., 2014; Boucher, Bigham, Mayes, & Muskett, 2008; Delobel-Ayoub et al., 2015; DeVilbiss et al., 2017; Fairthorne et al., 2017; Gardner et al., 2019; Grove et al., 2019; Hallett et al., 2013; Idring et al., 2014; Lee et al., 2015; Magnusson et al., 2012, 2016; Rai et al., 2013, 2017, 2018; Robinson et al., 2014; Schieve et al., 2015; Xie et al., 2017]. Due to sample size limitations, we were not able to conduct analyses stratified by time period. It is possible that cohort effects may have influenced results, since the distribution and influence of important factors, including diagnostic patterns, the environment and lifestyle, have changed between the generations during the study period. However, earlier studies (Sandin et al., using Swedish full population, and Taylor et al., in Swedish twins) found that estimates of heritability for ASD and for ASD traits across different

time periods exhibit only modest variability [Sandin et al., 2014; Taylor et al., 2020].

Another observation we made was that though the prevalence of ASD, especially that of ASD-ID exhibited male predominance, the familial risk profile between male and female index persons were very similar. This suggests that the higher male prevalence in ASD is likely to be more attributable to non-etiological factors such as diagnostic patterns than sex-specific etiological factors. However, since the aim of this study was on the familial risk and heritability of ASD with and without ID, our findings on the sex differences warrant future research and replication.

The access to a large, population-based, high-quality, prospectively collected data on ASD and ID outcomes and covariates is a main strength of this study. Medical care is free for children under the age of 18, and universal care is provided to all adults at low cost, reducing potential information bias due to differential access to health care due to economic status [Swedish Institute, 2018]. Ascertainment of a large number of families from population-based registers minimized selection bias. Multi-register data-linkage enabled ascertainment of extended families, so that we were able to estimate familial risks associated with different relations throughout the family tree.

As with most observational epidemiologic data, our study has some limitations. The diagnosis of ASD became available in 1987, so familial risk estimates of earlier born individuals might have been less accurate. However, since we stratified the familial risk analysis by relative type, the estimates of the more recently born individuals are not affected by this. To ameliorate this in the heritability analysis, we grouped the relatives by degree of relatedness to the index persons, not by relative type. Also, we restricted our sample to singletons, so it is important to note that our findings may not generalize to individuals from multiple births. We did not examine potential mediation by factors such as family psychiatric history. Due to the familial aggregation of psychiatric and neurodevelopmental disorders, it is likely that they share an etiology where genetic liability plays an important role. Also, it is possible that relatives of individuals with ASD who had similar difficulties were more readily diagnosed than relatives in unaffected families due to detection bias. Finally, there may be residual confounding; for example, ID may be underreported over time. Also, its reporting may be dependent on ASD diagnosis, both are untestable conditions.

Our study focused on the different ASD phenotypes as defined by presence or absence of ID. There are several considerations regarding issues with estimating heritability and its interpretation, as discussed by others [Tenesa & Haley, 2013]. The accuracy of heritability estimates depends on valid modeling assumptions. First, it should

be noted that our outcome is the presence of two outcomes, ASD and ID, since there is no ICD code for having both. Second, the calculations of heritability uses information in family types of different relatedness and assumes similar case ascertainment in all family types. We employed assumptions that may be simplistic, since we did not account for gene–environment interactions ($G \times E$), which growing evidence suggests is relevant for ASD [Kim et al., 2017; Lyall et al., 2017; Modabbernia, Velthorst, & Reichenberg, 2017]. Methods to estimate heritability while accounting for $G \times E$ are not well-established. Misspecification of heritability models by not accounting for $G \times E$ will lead to bias that could vary in direction. For example, if there is $G \times E$ and the risk environment is shared and the outcome is multifactorial (as commonly believed), then the model-estimated genetic contribution will be inflated [Cavalli-Sforza & Feldman, 1973; Lathrope, Lalouel, & Jacquard, 1984; Rao & Morton, 1974]. Accounting for $G \times E$ is an important limitation and needs to be addressed in future studies. Second, G and E generally are assumed to be independent and the covariance not modeled but if G and E are correlated in any way (for example, a maternal genotype increases likelihood of an environmental exposure that increases risk of the outcome), then estimates of heritability will be biased. These limitations and others are discussed further in Tenessa et al. [Tenessa & Haley, 2013].

There are also conceptual challenges to interpreting heritability. Heritability refers to how genetic variation relates to variation in phenotypic traits across a population and should not be interpreted as an absolute estimate of how much of a phenotype's occurrence is caused by genetics. It is possible that even with 100% heritability, the environment still substantially influences phenotype [Lewontin, 1974; Moore & Shenk, 2017]. Furthermore, in the $G \times E$ world of disease causation where genetic susceptibility factors and environment are both assumed to be at play, it may be philosophically nonsensical to disentangle the relative contributions of genes versus environment, when both may be necessary to cause disease. These arguments and other important ones are further described by Moore and Shenk [Moore & Shenk, 2017].

What then can the heritability estimates produced by our study tell us about the nature of ASD with and without ID? Heritability can still be assumed to correlate with genetic contribution (i.e., the more genetic a disease is, the higher the heritability estimates will be), so relative estimates of heritability can still be useful. It is difficult to compare between our study and others given the different biases that may be at play. However, comparing heritability estimates of ASD–ID and ASD+ID within our study may still be useful, since the similar biases would apply to both estimates. We believe that taken together,

the results from the heritability analysis and familial risk analysis suggest that ASD–ID may have a greater genetic basis than ASD+ID, although this should be verified in future studies. In conclusion, familial risk and heritability of ASD–ID may be higher than that of ASD+ID, which implies that risk factors between these phenotypes differ as well.

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Conflict of Interest

None.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Appendix S1. Heritability estimation.

Table S1. Odds Ratio of Autism Spectrum Disorders with and without Intellectual Disability in All Male and Female Index Persons with Relatives Affected by ASD, Compared to That in Index Persons of the Same Sex with Unaffected Relatives.

Table S2. Tetrachoric Correlations of Index Person's Autism Spectrum Disorders with and without Intellectual Disability with Family Relative's Autism Spectrum Disorders.